

What is claimed is:

1           1.     A composition comprising a hydrophilic portion and a hydrophobic  
2     portion joined by an ortho ester linker, wherein the ortho ester linker hydrolyzes at an  
3     increasing rate as the pH is reduced below 7.

1           2.     The composition of claim 1, wherein the hydrophilic portion comprises a  
2     polymer capable of increasing circulation time in the bloodstream of animals when  
3     incorporated on the surface of an encapsulator.

1           3.     The composition of claim 2, wherein the hydrophilic portion comprises  
2     methoxypolyethylene glycol.

1           4.     The composition of claim 2, wherein the hydrophilic portion is selected  
2     from the group consisting of polyethyleneglycol, hydroxylated dendrons,  
3     poly(methyloxazoline), poly(ethyloxazoline) and polyvinylpyrrolidone.

1           5.     The composition of claim 2, wherein the hydrophilic portion comprises  
2     polyethyleneglycol having a molecular weight from 200 to 20000.

1           6.     The composition of claim 1, wherein the hydrophilic portion comprises a  
2     targeting ligand.

1           7.     The composition of claim 1, wherein the hydrophilic portion comprises a  
2     cationic group.

1           8.     The composition of claim 7, wherein the cationic group is selected from the  
2     group consisting of primary amines, secondary amines, tertiary amines, quaternary  
3     ammoniums or imidazoles.

1           9.     The composition of claim 1, wherein the hydrophobic portion is selected  
2     from the group consisting of diacyl glycerols, distearoylglycerol, dipalmitoylglycerol,  
3     dimyristoyl glycerol, dioleoyl glycerol.

1           10.    The composition of claim 1, wherein the hydrophobic portion is selected  
2     from the group consisting of tocopherol, cholesterol, coenzyme Q, and ceramide.

1 11. The composition of claim 1, wherein the ortho ester linker comprises a  
2 diortho ester.

1 12. The composition of claim 11, wherein the ortho ester linker comprises a  
2 diketene acetal derivative.

1 13. The composition of claim 11, wherein the ortho ester linker comprises a  
2 3,9-dialkoxylated 3,9-Diethyl-2,4,8,10-tetraoxaspiro[5,5]undecane derivative.

1 14. The composition of claim 11, wherein the composition comprises 3,9-  
2 Diethyl-3-(2,3-distearoyloxypropyloxy)-9-(methoxypolyethyleneglycol2000-1-yl)-  
3 2,4,8,10-tetraoxaspiro[5,5]undecane.

1 15. The composition of claim 1, wherein the ortho ester linker comprises a  
2 single ortho ester.

1 16. The composition of claim 15, wherein the ortho ester linker comprises a  
2 dichloromethylmethyl ether derivative and the hydrophilic portion is cationic.

1 17. The composition of claim 16, wherein the composition comprises *N,N*-  
2 dimethyl-(4-methoxy-(cholest-5-en-3 $\beta$ -oxy)hept-3,5-dioxa-yl)ammonium (DOC).

1 18. The composition of claim 16, wherein the composition comprises  
2 *N,N,N*-trimethyl-(4-methoxy-(cholest-5-en-3 $\beta$ -oxy)hept-3,5-dioxa-yl)amine iodide.

1 19. A composition comprising an encapsulator, wherein the encapsulator  
2 comprises the composition of claim 1.

1 20. The composition of claim 19, wherein the encapsulator further  
2 comprises a lipid.

1 21. The composition of claim 20, wherein the lipid comprises DOPE.

1 22. The composition of claim 21, comprising DOPE/POD in a ratio of about  
2 97:3 to 85:15.

1           23.    The composition of claim 21, comprising DOPE/DOC.

1           24.    The composition of claim 20, wherein the lipid comprises a fusogenic  
2 lipid.

1           25.    The composition of claim 20, wherein the lipid comprises a lipid selected  
2 form the group consisting of phosphatidylcholine, phosphatidylglycerol,  
3 phosphatidylethanolamine, phosphatidylserine, phosphatidic acid, cholesteryl  
4 hemisuccinate, cholesterol sulfate, ceramide, cardiolipid, *N*[1-,2dioleoyl-3-  
5 trimethyl]ammonium propane (DOTAP), dimethyldioctadecylammonium bromide  
6 (DDAB), 1-palmitoyl-2-oleoyl-*sn*-glycero-3-ethyl-phosphocholine, *N*[1-(2,3-  
7 dioleyloxy)propyl]-*N,N,N*-triethylammonium (DOTMA), triglycerides, squalene,  
8 coenzyme Q and alkyl acylcarnitine esters.

1           26.    The composition of claim 20, wherein the lipid further comprises a  
2 targeting ligand.

1           27.    The composition of claim 26, wherein the targeting ligand is selected a  
2 group consisting of hyaluronan, antibodies, peptides, folate, receptor antagonists,  
3 carbohydrates, transferrin, protein hormones, and cytokines.

1           28.    The composition of claim 19, wherein the hydrophilic portion comprises  
2 a targeting ligand.

1           29.    The composition of claim 28, wherein the targeting ligand is selected a  
2 group consisting of hyaluronan, antibodies, peptides, folate, receptor antagonists,  
3 carbohydrates, transferrin, protein hormones, and cytokines.

1           30.    An encapsulator for delivering a compound, comprising an amphipathic  
2 low pH sensitive lipidic composition wherein the encapsulator exhibits degradation of  
3 less than 10% within 3 hours at a pH of 7.4 and degradation greater than 50%  
4 within 60 min at a pH of 5.0.

1           31.    The encapsulator of claim 30, wherein the amphipathic low-pH sensitive  
2 lipidic composition comprises a hydrophilic portion, a hydrophobic portion and an  
3 ortho ester linker.

1           32.    The encapsulator of claim 31, wherein the hydrophilic portion comprises  
2 PEG.

1           33.    The encapsulator of claim 32, wherein the ortho ester linker comprises a  
2 diketene acetal derivative.

1           34.    The encapsulator of claim 30, further comprising a lipid.

1           35.    The encapsulator of claim 30, wherein the lipid is selected from the  
2 group consisting of phosphatidylcholine, phosphatidylglycerol,  
3 phosphatidylethanolamine, phosphatidylserine, phosphatidic acid, cholesteryl  
4 hemisuccinate, cholesterol sulfate, ceramide, cardiolipid, *N*[1-,2dioleoyl-3-  
5 trimethyl]ammonium propane (DOTAP), dimethyldioctadecylammonium bromide  
6 (DDAB), 1-palmitoyl-2-oleoyl-sn-glycero-3-ethyl-phosphocholine, *N*[1-(2,3-  
7 dioleyloxy)propyl]-*N,N,N*,-triethylammonium (DOTMA), triglycerides, squalene,  
8 coenzyme Q and alkyl acylcarnitine esters, and dioleoylphosphatidyl ethanolamine  
9 (DOPE).

1           36.    The encapsulator of claim 33, wherein the hydrophilic portion comprises  
2 PEG, further comprising a lipid.

1           37.    The encapsulator of claim 30, wherein the ortho ester linker comprises a  
2 dialkoxy methoxy methine group

1           38.    A method for delivering a drug to a cell comprising the steps of  
2 providing an encapsulator comprising an LOC and the drug and administering the  
3 encapsulator.

1           39.    The method of claim 38, further comprising the steps of reducing pH,  
2 degrading the encapsulator and releasing the drug. Add support active lowering of  
3 pH

1 40. The method of claim 38 further comprising the steps of preparing a dry  
2 powder formulation of the encapsulator and administering the dry powder.

1 41. The method of claim 40, further comprising the steps of preparing a dry  
2 powder formulation of the encapsulator, rehydrating the encapsulator in an  
3 appropriate buffer and administering the encapsulator.

1 42. A method for incorporating an LOC into an encapsulator comprising the  
2 step of mixing the encapsulator with the LOC.

1 43. The method of claim 42, further comprising the steps of:

- 2 a) preparing a dry film of the LOC;  
3 b) rehydrating the LOC to form micelles; and  
4 c) combining the micelles with an encapsulator suspension.

1 44. The method of claim 42, wherein the encapsulator comprises a cationic  
2 lipoplex further comprising the steps of preparing a cationic lipoplex and coating the  
3 lipoplex with the LOC.

1 45. The method of claim 42 further comprising the steps of:

- 2 a) preparing a dry film of the LOC;  
3 b) preparing an encapsulator suspension; and  
4 c) combining the encapsulator suspension with the dry film.

1 46. The method of claim 42, further comprising the steps of :

- 2 a) preparing the LOC in a non-aqueous, water miscible solvent  
3 b) preparing an encapsulator suspension; and  
4 c) combining the encapsulator suspension with the LOC in the water  
5 miscible solvent.

1 47. The method of claim 46, wherein the non-aqueous, water miscible  
2 solvent is selected from the group consisting of acetonitrile, dimethylsulfoxide,  
3 glyme, methylpyrrolidone, ethanol, triacetin and mixtures of these.

1 48. A method for storing an encapsulator for delivering a compound,  
2 comprising the steps of:

3 a) providing an encapsulator comprising an amphipathic low pH sensitive  
4 lipidic compound wherein the encapsulator exhibits degradation of less than 10%  
5 within 3 hours at a pH of 7.4 and degradation greater than 50% within 60 min at a  
6 pH of 5.0; and

7 b) lyophilizing the encapsulator.

1 49. The method of claim 48, further comprising the step of milling the  
2 lyophilized encapsulator to form a dry powder.

1 50. A method for gene transfer comprising the steps of:

- 2 a) providing encapsulator comprising an amphipathic low pH sensitive  
3 lipidic composition and a polynucleotide;  
4 b) administering the encapsulator to an animal;  
5 c) reducing the pH to degrade the encapsulator; and  
6 d) releasing the polynucleotide.

1 51. The method of claim 50, further comprising the step of forming a dry  
2 powder formulation from the encapsulator prior to administering the encapsulator.

1 52. The method of claim 51, further comprising the step of rehydrating the  
2 encapsulator prior to administering the encapsulator.